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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/515,260	02/29/2000	Dasa Lipovsek	50036/021003	1893

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EXAMINER

SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 06/18/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

**FILE COPY****Office Action Summary**

Application No.

09/515,260

Applicant(s)

LIPOVSEK ET AL.

Examiner

Holly Schnizer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 March 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-44 and 51-68 is/are pending in the application.
- 4a) Of the above claim(s) 1-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 40-44 and 51-68 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Status of the Claims***

1. The Amendment filed March 15, 2002 (Paper No. 11) has been entered and considered. Claims 45-50 have been cancelled and Claim 68 has been added. Therefore, Claims 1-44 and 51-68 are pending. Claims 1-39 are withdrawn from further consideration as being drawn to a non-elected invention. And, Claims 40-44 and 51-68 have been considered on the merits in this Office Action.

### ***Drawings***

The drawings filed March 15, 2002 have been entered. However, the drawings are missing from the application. The examiner respectfully requests new drawings to be placed in the file in response to this Office Action and apologizes for any inconvenience this may cause.

### ***Rejections Withdrawn***

The rejection of Claims 40-42 under 35 U.S.C. 112, second paragraph because the term "randomized" unclear is withdrawn in light of the amendment of the claims indicating that the "randomized loop" occurs in a library of proteins.

The rejection of Claims 40-67 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

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application was filed, had possession of the claimed invention is withdrawn in light of Applicant's arguments.

The rejection of Claims 48-50 under 35 U.S.C. 112, first paragraph for lacking enablement for a method wherein compound binding is mediated by one, two, or three loops of the tenth module of the fibronectin type III domain is withdrawn in light of the cancellation of these claims.

The rejection of Claims 40-47, 49, 52, 59, and 66 under 35 U.S.C. 102(a) as being anticipated by Koide et al. (J. Mol. Biol. (1998) 284: 1141-1151; referenced in IDS of Paper No. 5) is withdrawn in light of Applicants argument that the full journal article was not available until December 11, 1998, after the priority date of the present application. In addition, Koide et al. do not teach obtaining a scaffold-based protein specifically having at least three randomized loops.

The rejection of Claims 40-41, 44-46, 56-57, and 59-61 under 35 U.S.C. 103(a) as being unpatentable over Main et al. (Cell (1992) 71: 671-678; referenced in IDS of Paper No. 3) in view of Lee et al. (Protein Engineering (1993) 6: 745-754) and Nygren et al. (Curr. Opin. Struct. Biol. (1997) 7: 463-469; referenced in IDS of Paper No. 3) is withdrawn in light of the amendments to the claims. The Main et al., Lee et al., and Nygren et al. reference do not teach or provide motivation to specifically randomize at least three loops in the methods taught therein.

***Rejections Maintained***

***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 40-44 and 51-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 40-44 and 51-68 remain unclear as to what sequences are considered randomized since the claims do not contain a template sequence with which to compare. Applicants argue that the claims have been amended to specify that the claimed proteins are scaffold based proteins and that the scaffold is the tenth module of the human fibronectin type III domain, the template sequence of which was known in the art at the time of filing. This argument has been considered but is not deemed persuasive for the reasons provided in the previous Office Action (Paper No. 8). The specification defines randomized as "including one or more amino acid alterations relative to a template sequence (see p. 9, lines 1-2). Many proteins contain fibronectin type III domains and the amino acid sequences of these domains vary even within one species. Thus, for example, one might view tenascin (comprising a type III domain) as a protein within the metes and bounds of the claims because it contains loops having amino acid alterations (randomized) as compared to a particular fibronectin sequence. On the other hand, another might view tenascin outside the metes and bounds of the claims because as compared to its own fibronectin type III domain, there are no amino

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acid alterations (no randomized loop). It is noted that specification that the amendment specifying that the fibronectin type III domain is "human" does not overcome the rejection because the human fibronectin type III domain also may have many different sequences (see Main et al. Cell, Vol. 71, pp. 671-676 (IDS of Paper No. 3), at Figure 3, page 674). Addition of a template sequence with which to determine if a loop was randomized would clarify this matter.

Claim 59 remains unclear because the term "randomized" still refers to a single proteins. As stated in the previous Office action, one of skill in the art would understand "randomized" to mean that individual proteins of a library contain unique sequences relative to other proteins of the library. It is not art recognized to refer to sequences as randomized unless they are compared to sequences of other related proteins. For example, Koide et al. (J. Mol. Biol. (1998) 284: 1141-1151; reference in IDS of Paper No. 5) states that they prepared a library of FN3 in which residues in two loops were randomized (see abstract). Claim 59 still refers to randomized loops of a single protein without comparison to another protein sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 41, 43, and 44, as amended, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining a

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protein or compound which binds a protein or compound comprising contacting a protein comprising a fibronectin type III domain having at least one randomized loop under conditions that allow complex formation and obtaining the protein or compound from the complex, does not reasonably provide enablement for such a method wherein binding ability results from randomization of at least three loops of the tenth module of the fibronectin type III domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. Claims 41, 43, and 44 are rejected for the same reasons as given for claims 48-50 in the previous Office Action. In response to the Office Action, Applicants cancelled the rejected claims and indicated that claim 41 does not require that compound binding be "mediated" by the randomized loops. However, Claim 41, as amended, recites "wherein the binding ability results from the randomization of said at least three loops" in line 7-8 of the claim. As stated in the previous Office Action, the specification has not taught how to practice the claimed method wherein the number of loops that are involved in binding can be predicted or controlled. Protein binding is dependent on structure. And, the state of the art is such that it is acknowledged that one cannot merely predict protein function (such as binding function) from amino acid sequence information. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation that they will provide a particular binding function is unpredictable. (see Wells, 1990, Biochemistry 29:8509-

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8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 14-16).

Thus, even using library screening techniques, one of skill in the art would not know which loops and which amino acid positions within those loops should be randomized to achieve binding through a specific number of loops. Claims 43 and 44 are dependent from Claim 41 and therefore encompass this limitation. Therefore, it appears that the present specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with Claims 41, 43, and 44.

### **New Rejection**

#### ***Claim Rejections - 35 USC § 112***

Claims 40, 42, 44, 51, 53-56, and 58 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps involved in obtaining a protein with at least three randomized loops (see last line of Claim 40) from a library of proteins having only one or two randomized loops (see line 5 of Claim 40). Correction is required. Amending Claim 40, line 5, to recite "said scaffold-based proteins having at least three randomized loops" would overcome this rejection.



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### **Conclusions**

No Claims are allowable. However, the claimed methods appear to be free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Holly Schnizer  
June 17, 2002



**CHRISTOPHER S. F. LOW  
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